IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re United States Patent Application of:		**Docket No.:**	**4240-138**
Applicants:	**KIM, Jung Moon, et al.**	**Conf. No.:**	**9719**
Application No.:	**10/560,329**	**Art Unit:**	**1609**
Date Filed:	**December 10, 2005**	**Examiner:**	**Stacey Nee MacFarlane**
Title:	**NON-ACTIVATED POLYPEPTIDES HAVING A FUNCTION OF TISSUE REGENERATION AND METHOD FOR PREPARING THE SAME**	**Customer No.:**	**23448**

CERTIFICATE OF EFS FILING

I hereby certify that this document is being filed via EFS in the United States Patent and Trademark Office on **August 11, 2008.**
/kelly k. reynolds/

RESPONSE TO APRIL 10, 2008 FINAL OFFICE ACTION AND PETITION FOR EXTENSION OF TIME IN U.S. PATENT APPLICATION NO. 10/560,329

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

In response to the Final Office Action mailed April 10, 2008, please enter this Amendment and Response into the file of the above-identified application.

The time for responding to the April 10, 2008, Final Office Action without extension was set at three months, or July 10, 2008. Applicants hereby request a one (1) month extension of time under 37 CFR § 1.136 to extend the deadline for response to August 10, 2008. Because August

10, 2008 fell on a Sunday, such deadline is automatically extended to **Monday, August 11, 2008** through the operation of 37 CFR 1.7.

Reconsideration of the application in view of the ensuing remarks set out below is respectfully requested.

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REMARKS

Regarding the Response

No claims have been amended by the present Response. Thus, upon entry of the Response, claims 1, 2, 5-20, and 23-28 will be pending, of which claims 10-17 are withdrawn.

Rejection of Claims 1-9 and 18-28 Under 35 U.S.C. §103

In the Final Office Action mailed April 10, 2008, the examiner has rejected claims 1-9 and 18-28 under 35 U.S.C. § 103(a) as unpatentable over Published U.S. Patent Application No. 2004/0197867 (hereinafter "the '867 publication"), further in view of U.S. Patent No. 5,013,649 (hereinafter "the '649 patent") and Leighton, M., et al., J. Biol. Chem., (2003) p. 18478-18484, vol. 278, n. 20 (hereinafter "Leighton et al.").

In the Final Office Action at page 3, the examiner has stated that applicants' previous arguments were not persuasive. In response, applicants provide the following.

On page 3 of the Final Office Action, the examiner states that "the '649 Patent and Leighton reference had already disclosed that it was known in the art that the 'furin activation domain' (FAD), comprising an amino acid sequence of the instantly-elected SEQ ID NO: 14, fused with the 'tissue regeneration domain' (TRD), comprising an amino acid sequence of the instantly-elected SEQ ID NO: 1, is the equivalent of the hBMP proprotein." The examiner also states that the '867 publication discloses a structure of PTD-BMP2 peptide (Final Office Action, p. 4), and that in view of the combination of the cited references, the present application is rendered obvious. Applicants respectfully disagree.

It is elemental law that in order for an invention to be obvious, the difference between the subject matter of the application and the prior art must be such that the subject matter as a whole would have been obvious at the time the invention was made to a person of ordinary skill in the art. In order to meet this standard for a proper §103 rejection, all claim limitations must be disclosed or derivable from the cited combination of references, there must be a logical reason to combine the cited references to produce an operable combination and there must be a reasonable expectation of success (*see* MPEP §2143).

The claims of the application that are pending and under examination recite a polypeptide (claims 1, 2, 5-9) and compositions (claims 18-20 and 23-28). All of the composition claims depend directly or indirectly on the polypeptide of claim 1. Therefore all pending claims of the present application recite a polypeptide (TRP) that comprises a PTD, a FAD and a TRD. However, it is noted that the claims are not simply structural recitations, but also comprise functional description, where the TRP is activated by cleavage of the FAD and which stimulates the growth or formation of tissues or to induce the regeneration of tissues. Therefore structural recitations that are similar to those of the claims, but do not possess the claimed activity are not encompassed by the claims. Similarly, cited references showing a similar structure must also possess the recited function in order to render the claimed invention obvious.

The examiner's attention is respectfully drawn to pages 18482-18483 of Leighton et al., where it is described that prodomain cleavage by a furin is important for the activation of BMP-1 in a process of activation and secretion of proBMP-1. However, Leighton also state that in the absence of prodomain cleavage, BMP-1 protein is still secreted. These descriptions, to one of skill in the art, would therefore remove the motivation to introduce proBMP polypeptide into cells, when BMP-1 is similarly secreted, in order to obtain an effect such as tissue regeneration.

Additionally, Leighton et al. disclose an intracellular biosynthesis and a post-translational modification in the trans-Golgi network, but the present invention relates to introduction of a protein having its 3-dimentional structure removed, which is synthesized in a laboratory, into a cell. Unlike the intracellular biosynthesis described in Leighton et al., prior to the present invention, the intracellular process in activating a protein introduced into a cell, such as that described in the present invention was unknown. For this reason, it cannot be said that one of skill in the art would be motivated to obtain the presently claimed polypeptide from the activation of BMP protein synthesized in the cell as disclosed in Leighton et al.

Additionally, the '649 patent describes a method for producing purified BMP-2 through an intracellular process by inserting a DNA sequence into cell. Specifically, the '649 patent simply describes obtaining mature BMP protein by inserting a proBMP-encoding gene, not proBMP protein, into a cell to biosynthesize mRNA from a gene expressing BMP-2 introduced into a specific cell, transferring the mRNA to the cytoplasm, biosynthesizing a protein using the mRNA in ribosome and extracellularly secreting the synthesized protein through post-translational modification. In other words, the '649 patent does not suggest that extracellularly synthesized proBMP protein be directly inserted into a cell.

Despite the fact that the amino acid sequence of the polypeptide described in the present invention is similar to that of the polypeptide described in the '649 patent, its secondary and tertiary structure and its functional mechanisms as well as the method for preparing it are quite different from those of the polypeptide described in the '649 patent. The examiner's attention is again respectfully drawn to the claims, wherein claim 1 recites the characteristic of the claimed polypeptide that it "stimulate the growth or formation of tissues or to induce the regeneration of tissues." Claims 2, 5-9, 18-20 and 23-28 depend directly or indirectly from claim 1 and likewise require such distinguishing features. Accordingly, the TRD required by such claims has completely different physical and chemical characteristics compared to the polypeptide of the '649 patent.

Therefore, one of skill in the art would not have been motivated to substitute proBMP protein for BMP protein in the structure of PTD-BMP protein in the '867 publication by combining the '649 patent and Leighton et al. Accordingly, the combination of references does not describe either a combination of a prodomain-containing BMP and a PTD, nor does the combination of references describe insertion of such a polypeptide into a cell.

Furthermore, on page 4 the examiner states that "[t]he reference [the '867 publication] discloses BMP2 fused with the PTD of TAT. Experimental data is not necessary for anticipation of the polypeptide." In addition, the examiner cites the applicants as arguing "that the '867 publication 'asserts that bone formation will be induced' (Remarks page 11, paragraph 1) but that the reference does not correctly describe the mechanisms by which PTD-BMP would achieve this result" and that "the '867 publication fails to suggest intracellular delivery of the fusion protein, but that 'the present invention concretely suggests transfer of secreted protein BMP to cells, the processes of cleavage and activation by furin in cells and the secretion of activation protein'". In reply, the examiner "asserts that any results such as bone regeneration, intracellular delivery, and protein activity are merely inherent features of the fusion polypeptide product..."

Applicants respectfully disagree. As stated above, the functional aspect of the claimed polypeptide is an essential feature of all of the claimed polypeptides and compositions of the present application. Indeed, the activity of all polypeptides with the structure recited in claim 1 cannot be said to have the same functional activity and the functional activity recited in the claims is not inherent in all structures such as those recited in claim 1.

From the results of Example 1 in the description of the present invention, it can be seen that PTD-hBMP (as described in the '867 publication) has cell permeability but its insertion does not provide the effect of inducing bone formation or for secreting mature BMP-2 protein which has the ability of inducing bone formation. (Specification, p. 25, lines 24-28; page 28, lines 4-20). This result is expected in view of the fact that a secretory protein having physiological activity, such as BMP-2, needs to undergo proper cellular processes such as various post-translational modifications after it is synthesized in a cell in order to have such activity.

Therefore, the PTD-BMP of the '867 publication is PTD with mature BMP-2, and the present application suggests in Example 1 that such structure has no biological activity. Thus, contrary to the examiner's statement, bone regeneration, intracellular delivery and protein activity **are not** "inherent features of the fusion polypeptide product."

Additionally, it cannot be said that the '867 publication is predictive of the product according to the present invention. The present invention suggests that proteins can have various biological activities and permeability into a cell, depending on their secondary and tertiary structure even if the proteins have the same amino acid sequences, which is an important feature of the present invention. However, the '867 publication provides no prediction or description with respect to activity and/or permeability dependent on structure.

Furthermore, the examiner states that "[e]xperimental data is not necessary for anticipation of the polypeptide" regarding the '867 publication. Applicants respectfully disagree.

The '867 publication provides the following:

> An increase in the expression of LMP, intracellular protein increase the expression of mature BMP-2, and the mature BMP-2 is secreted extracellularily to bind with a receptor in cell membrane, thus activating SMADs signal transduction.

Based on such reasoning, the '867 publication suggests that LMP, BMPs and SMADs will be used to induce bone formation by combining with PTD. However, SMADs have a plurality of down-stream genes involved in bone formation and each down-stream gene also regulates other thousands of genes. Consequently, the examiner's statement would therefore be applicable to anticipation of the combination of thousands of genes with PTD with no requirement of experimentation.

Additionally, since the '867 publication suggests that both SMADs for inducing bone formation

and other SMADs for inhibiting bone formation are used for bone-formation polypeptide technique, it cannot be said that the '867 publication renders the subject matter of the present claims obvious.

As is demonstrated in Example 2 of the present invention, the fusion protein according to the present invention is activated by furin, despite the lack of a signal peptide. This means that the fusion protein according to the present invention has different intracellular processing from BMP biosynthesized in cells to be secreted. Signal peptide plays a role of transferring the BMP synthesized in ribosome to endoplasmic reticulum (ER) and Golgi when BMP is biosynthesized in cells, and this process is essential for secreting proteins having biological activity (Sakaguchi M., Curr. Opin. Biothecnol., 8:595, 1997). However, as in Example 4 of the present invention, the fusion protein according to the present invention has higher activity in case of the absence of signal peptides. In other words, it does not need such processes.

Additionally, the proteins biosynthesized in cells have their inherent secondary and tertiary structure by various molecular interactions, in particular hydrogen bond and disulfide bond (Branden C. & Tooze J., Introduction to protein structure, 2nd Ed. 1999, Garland Publishing, USA). In addition, as stated by the examiner, because the protein such as BMP has RX(K/R)R furin cleavage motif, the cleavage of prodomain consequently occurs before BMP is secreted out of the cell. However, this intracellular processing is possible under the assumption that the protein has its own secondary and tertiary structure, which is obvious to one skilled in the art, so Leighton et al. do not describe this. However, although the polypeptide of the present invention has the same amino acid sequences as described above, it has no secondary and tertiary structure because of denaturing process by Urea. Therefore, although the polypeptide of the present invention has RX(K/R)R furin cleavage motif, it cannot be said that the processing described in Leighton et al. would naturally occur. That is to say, since the processing as described in the Leighton et al. can be carried out only after all the processes such as intracellular pemeation into cells, escape from lipid raft, exposure to water environment and restructuring of PTD-BMP, are successfully preceded. Therefore, it cannot be said that, without experimental basis, Leighton et al. provide any motivation to complete the present invention.

Therefore, since Leighton et al. just suggest the intracellular biosynthesis mechanism regarding BMP, it cannot be said that there is the motivation to derive the claimed invention.

The present inventors recognized the problems in the prior art that the clinical application of the commercially available conventional hBMPs has been limited because of extremely high cost and inconveniences due to activity loss thereof in storage, handling and administration, and undertook efforts to develop a polypeptide having a novel biochemical structure and pharmaceutical mechanism, which has low production cost, is convenient in storage, handling, and does not cause a reduction in its activity in administration steps, thus resulting in the present invention. The present invention is based on the new finding **that in the case of providing the fusion polypeptide of PTD-FAD-TRD, it is much easier to prepare, store, handle and administer such fusion polypeptide because it is no longer necessary to maintain TRD as an active structure.**

However, Leighton et al. just describe that the removal of prodomain activates proteinase (Abstract). The '649 patent just suggests the method for producing purified BMP-2. Both references relate to a method for providing active BMP and they do not have the same objective or subject matter as the present invention.

Additionally, the '867 publication provides that the bone formation will be induced when LMP, which is PDZ-LIM protein, is recombined with PTD (protein transduction domain) and then administered, based on which it suggests that when LMP-1 is overexpressed in culture cells by using adenovirus the expression of intracellular mRNA is increased, and the level of intracellular BMP-2 and BMP-7 proteins is increased ('867 publication, FIG. 2). However, the '867 publication does not show recognition and a solution regarding the problem of the inconvenience in the production, storage, handling, and administration of active BMP.

As the '867 publication in view of the '649 patent and Leighton et al. does not provide any logical basis for the polypeptide or composition recited in claims 1-9 and 18-28 , the '867 publication in view of the '649 patent and Leighton et al. does not render the claimed invention obvious. Accordingly, withdrawal of the rejection of claims 1-9 and 18-28 under 35 U.S.C. § 103 (a) as being obvious over the '867 publication in view of the '649 patent and Leighton et al. is respectfully requested.

CONCLUSION

Based on the foregoing, all of Applicants' pending claims 1-9 and 18-28 are patentably distinguished over the art, and are in form and condition for allowance. The Examiner is requested to favorably consider the foregoing and to responsively issue a Notice of Allowance.

The time for responding to the April 10, 2008 Office Action without extension was set at three months, or July 10, 2008. Applicants hereby request a one (1) month extension of time under 37 C.F.R. § 1.136 to extend the deadline for response to and including August 11, 2008. Payment of the extension fee of $60.00 specified in 37 C.F.R. § 1.17(a)(1), as applicable to small entity, is being paid by on-line credit card payment at the time of EFS submission of this Response. Should any additional fees be required or an overpayment of fees made, please debit or credit our Deposit Account No. 08-3284, as necessary.

If any issues require further resolution, the Examiner is requested to contact either of the undersigned attorneys at (919) 419-9350 to discuss same.

Respectfully submitted,

Date: August 11, 2008

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